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1 401 549

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(31) Convention Application No. 36901/73 (32) Filed 29 March 1973
(31) Convention Application No. 39175/73 (32) Filed 4 April 1973 in
(33) Japan (JA)

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(54) PYRIDO[2,3-d]PYRIMIDINE-2,4(1H,3H)-DIONES AND METHODS OF PREPARING THEM

(71) We, HISAMITSU PHARMACEUTICAL CO., INC., a Company organised according to the laws of Japan, of No. 408, Tashiro-daikan-machi, Tosu-shi, Saga-ken, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to pyrido[2,3-d]pyrimidine-2,4)1H,3H)-diones and to methods of preparing them.

Numerous compounds for use as anti-inflammatory agents, analgesics and central nervous system depressants are known, such as phenylbutazone, flufenamic acid, mefenamic acid, aminopyrine, diazepam, nitrazepam, and methaqualone. These medicines, however, are often insufficiently effective or present such side reactions as gastroenteric trouble, dermatitis, renal paralysis, nausea, dizziness, tinnitus and drowsiness, and so superior anti-inflammatory agents, analgesics and central nervous system depressants are being sought.

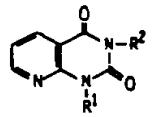
The compounds of the present invention have been shown to have anti-inflammatory, analgesic, antiulcerous, antipyretic, antihistaminic and central nervous system depressive activities without presenting substantial toxicity and to be remarkably useful as anti-inflammatory agents, analgesics and central nervous system depressants.

U.S. Patents Nos. 3,272,816 and 3,296,447 discloses 7-amino-2,4-dioxo-1,2,3,4-

[Price 33p]

tetrahydropyrido[2,3-d]pyrimidines, but the compounds of the present invention, which have no amino radical in position-7 and are also different in the structure of other side chains, are superior to the above compounds in anti-inflammatory, analgetic and central nervous system depressive activities.

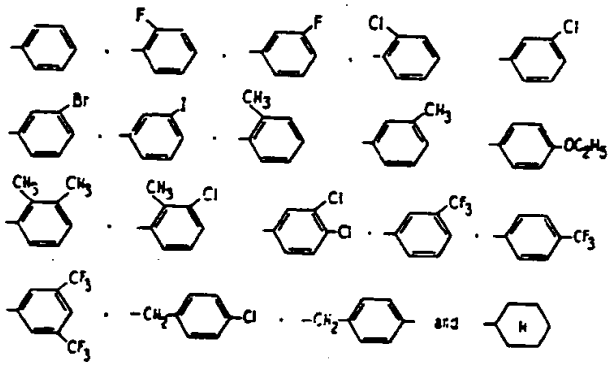
According to the present invention there are provided pyrido[2,3-d]-pyrimidine-2,4(1H,3H)diones represented by the general formula [A]:

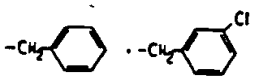
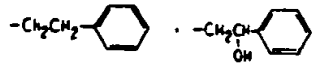
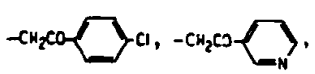


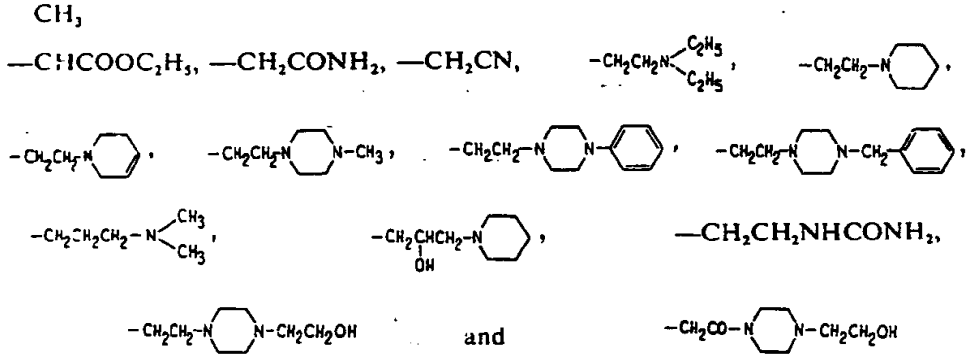
[A]

wherein R^1 denotes an aryl or aralkyl group or a cyclohexyl radical, and R^2 denotes a hydrogen atom or an alkyl, substituted alkyl, unsaturated hydrocarbon, alkoxycarbonyl or substituted unsaturated alkyl group.

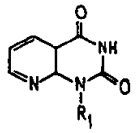
Preferably R^1 is selected from



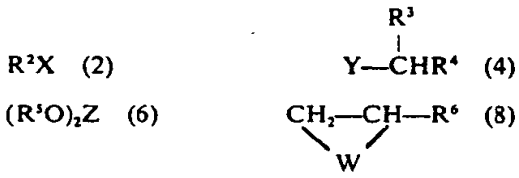
and R^2 is selected from —H, —CH_3, —C_2H_5, —$CH_2CH_2CH_3$, —$CH<^{CH_3}_{CH_3}$, —$CH_2CH_2CH_2CH_3$, —$CH_2CH<^{CH_3}_{CH_3}$, CH_2CH_2Cl, —CH_2CH_2Br, —$CH_2CH_2CH_2Cl$, —$CH_2CH=CH_2$, —$CH_2C(CH_3)=CH_2$, —$CH_2CH=CHCl$, —$CH_2C\equiv CH$, —CH_2CH_2OH, —$CH_2CH_2CH_2OH$, —CH_2CHCH_3 (OH), —CH_2CHCH_2OH (OH), —CH_2CHCH_2Cl (OH), —$CH_2CH_2OCOCH_3$, —CH_2OCH_3, —$CH_2OC_2H_5$, —$CH_2CH_2OC_2H_5$, —$CH_2CH_2OCH=CH_2$, —$CH_2CH_2OCH_2CH_2OH$, —$CH_2CHOC_2H_5$ (Cl), —CH_2—CH(O)—CH_2,  ,  , —CH_2COCH_3,  , —$COOC_2H_5$, —CH_2COOH, —$CH(CH_3)COOH$, —$CH_2COOC_2H_5$.



Further according to the present invention there is provided a method of preparing a compound of general formula [A], comprising reacting a compound of the general formula (1):

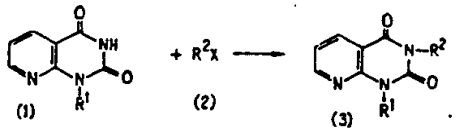


wherein R_1 is the same as in formula [A], with a compound selected from those of the general formulae (2), (4), (6), (8) and (10):



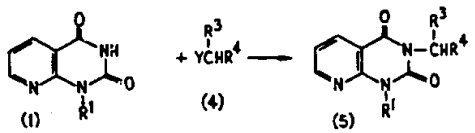
wherein R^2 is the same as in the formula [A], X denotes a halogen atom or an arylsulfonlyloxy group, R^3 denotes a hydrogen atom or a lower alkyl group, R^4 denotes a carbamoyl, cyano radical or an alkoxycarbonyl group, Y denotes a halogen atom, R^5 denotes a lower alkyl, a substituted alkyl or unsaturated hydrocarbon group, Z denotes a carbonyl (—CO—), sulfonyl ($—SO_2—$) or oxalyl (—CO—CO—) group, R^6 denotes a hydrogen atom, a lower alkyl, halogenated lower alkyl, lower unsaturated hydrocarbon or aryl group, W denotes an oxo (—O—), carbonyldioxo (—O—CO—O—) or sulfinyldioxo (—O—SO—O) group, and R^7 denotes a lower alkyl group.

Reaction scheme [I]:



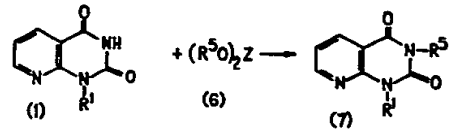
Examples of general formula (2) include ethyl iodide, propargyl bromide, allyl bromide and ethyl benzenesulfonate.

Reaction scheme [III]:



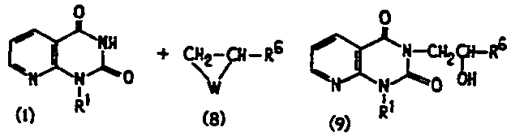
Examples of general formula (4) include ethyl chloroacetate, chloroacetamide and chloroacetonitrile.

Reaction scheme [III]:



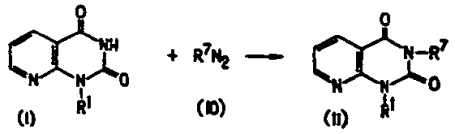
Examples of general formula (6) include demethylsulfate, diethyl carbonate and diethyl oxalate.

Reaction scheme [IV]:



Examples of general formula (8) include glycol sulfide, epichlorohydrin, propylene oxide and ethylene carbonate.

Reaction scheme [V]:



Examples of general formula (10) include diazomethane and diazoethane.

The starting materials, 1-substituted-pyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione derivatives as represented by general formula (1), are prepared in excellent yield when 2-aminonicotinamide derivative is reacted with diethyl carbonate in the presence of sodium ethylate.

The starting materials as represented by general formula (1) may be reacted with the aforesaid reagents of general formulae (2), (4), (6), (8), and (10). These reactions are preferable carried out in a solvent such as toluene, xylene, tetrahydrofuran, dioxane or dimethylformamide. The reactions as shown in the schemes [I], [II] and [III] should preferably be carried out in the presence of a metallic compound such as sodium alcoholate, sodium amide or sodium hydride or an inorganic salt such as an alkali hydroxide or carbonate. The employment of the said metallic compounds is particularly advantageous because a high yield of the object product is obtained.

The reaction temperature is not critical, but may be ambient or elevated. Since the reaction develops very rapidly, room temperature is sufficient for the reaction and heating is not necessary. The period of reaction may range from 30 min. to 3 hours, and may be shortened by heating mildly. On the other hand, when an oxalic acid diester or a dialkyl carbonate is employed as an N-alkylation agent in reaction scheme [III], the reaction should preferably be carried out in an autoclave at a temperature of 150—240°C.

The reaction solvent may be distilled off from the reaction-mixture and the residue mixed with water to precipitate crystals of the target compound. Then the crystals obtained may be easily recrystallized from methanol or a similar solvent for purification.

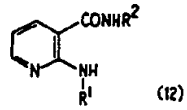
The compound obtained may be further converted into an addition salt combined with an inorganic or organic acid. Popular examples of such addition salts include the hydrochloride, sulfate, phosphate, acetate, benzoate, lactate, succinate, citrate, tartrate, fumarate, malonate and maleate. These salts are included within the scope of the present invention and this conversion into salts serves to improve the solubility and stability of the products.

In the above reaction scheme [II], in which the compound of general formula (5) produced by the reaction of compound (1) with compound (4) contains as R^4 a carbamoyl, cyano radical or an alkoxycarbonyl group, these compounds of

formula (5) may further be hydrolyzed, if desired, either by an alkali such as caustic alkali or alkali carbonate or by an acid such as hydrochloric, sulfuric or acetic acid into fatty acid derivatives.

In reaction scheme [IV], the reaction may proceed in a basic solvent at room temperature, but the reaction is finished in a short time when heated. On the other hand, in reaction scheme [V], the reaction is finished without any catalyst in an inert solvent when allowed to stand at room temperature.

Still further according to the present invention there is provided a method of preparing the compounds of general formula [A] comprising reacting a compound of the general formula (12):



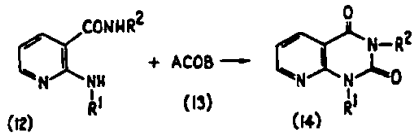
(12)

wherein R^1 and R^2 are the same as in formula [A], with a compound of the general formula (13):

$$ACOB \qquad (13)$$

wherein A and B may be the same or different and each represents a halogen atom, a lower alkoxy or amino group, or an imidazolyl radical.

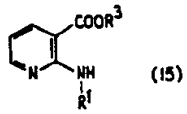
Reaction scheme [VI]:



(12) (13) (14)

Examples of general formula (13) include urea, methylurea, diethylurea, N-propylurethane, 1,1-carbonyldiimidazole, phosgene, ethyl chlorocarbonate and diethyl carbonate.

Yet another aspect of the present invention provides a method of preparing the compounds of general formula [A], comprising reacting a compound of the general formula (15):



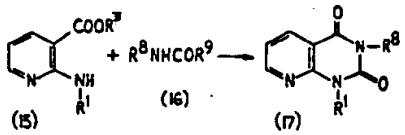
(15)

wherein R^1 is the same as in the formula [A] and R^3 is the same as in formula (4), with a compound of the general formula (16):

$$R^8NHCOR^9 \qquad (16)$$

wherein R^8 denotes a hydrogen atom or a lower alkyl or lower unsaturated hydrocarbon group and R^9 denotes an amino or lower alkoxy group.

Reaction scheme [VII]



(15) (16) (17)

Examples of general formula (16) include urea, diethylurea and N-propylurethane.

The reactions of these schemes [VI] and [VII] proceed smoothly under similar conditions, generally in an organic solvent such as dimethylformamide, diglyme, tetrahydrofuran or alcohol, but the reactions are preferably performed in the

presence of a metallic compound such as metallic sodium, sodium amide or sodium hydride, or in the presence of an organic base such as trialkylamine or pyridine or an inorganic base such as alkali hydroxide or carbonate. The first-mentioned metallic compounds are most effective in enhancing the yield of the product. The reaction temperature is not critical and may be either ambient or elevated. However, at a temperature of 50—120°C, the reaction time is shortened. The reaction solvent is distilled off from the reaction mixture, and the residual crystals are refined by recrystallization from a solvent such as methanol.

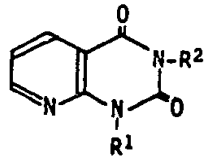
The compound obtained may further be converted into an inorganic salt such as the hydrochloride, phosphate or sulfate or an organic salt such as the acetate, lactate, succinate, tartrate, fumarate or maleate by a conventional technique.

Compounds:

The compounds of the present invention can be prepared by one of those processes as described in Reaction Series [I] to [VII]. Some examples of these compounds and their melting points are shown in Table I.

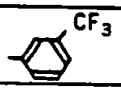
Table I

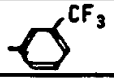
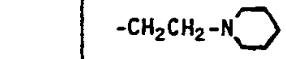
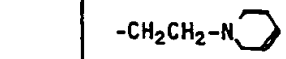
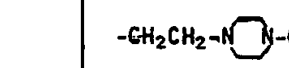
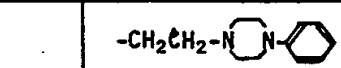
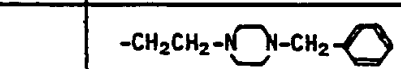
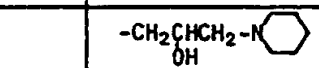
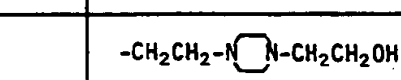
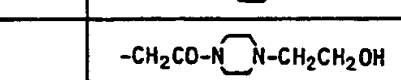
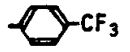
The Examples of the Compounds Obtained by the Present Invention

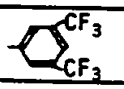


[A]

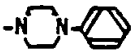
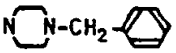
Compound No.	R^1	R^2	Melting point(°C)
1		-H	259-260
2	〃	$-CH_3$	224-225
3	〃	$-C_2H_5$	160-161
4	〃	$-CH_2CH_2CH_3$	139-140
5	〃	$-CH\begin{<}CH_3\\CH_3\end{}$	151-153
6	〃	$-CH_2CH_2CH_2CH_3$	153-154
7	〃	$-CH_2CH=CH_2$	135-136
8	〃	$-CH_2\overset{CH_3}{\overset{\vert}{C}}=CH_2$	130-131
9	〃	$-CH_2CH=CHCl$	134-135
10	〃	$-CH_2C\equiv CH$	177-178
11	〃	$-CH_2CH_2Cl$	167-168
12	〃	$-CH_2CH_2Br$	158-160
13	〃	$-CH_2CH_2CH_2Cl$	142-143
14	〃	$-CH_2CH_2OH$	142-143
15	〃	$-CH_2CH_2CH_2OH$	116-117
16	〃	$-CH_2\underset{\vert}{CH}-CH_3$ $\quad\quad OH$	169-170

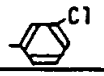
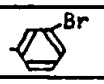
Compound No.	R^1	R^2	Melting point(°C)
17		$-CH_2\underset{OH}{CH}-CH_2OH$	170-171
18	〃	$-CH_2\underset{OH}{CH}-CH_2Cl$	156-157
19	〃	$-CH_2CH_2OCOCH_3$	140-141
20	〃	$-CH_2OCH_3$	135-136
21	〃	$-CH_2OC_2H_5$	162-163
22	〃	$-CH_2CH_2OC_2H_5$	140-141
23	〃	$-CH_2CH_2OCH=CH_2$	150-152
24	〃	$-CH_2CH_2OCH_2CH_2OH$	135-136
25	〃	$-CH_2\underset{Cl}{CH}OC_2H_5$	126-128
26	〃	$-CH_2-\underset{O}{CH}-CH_2$	161-163
27	〃		171-172
28	〃		146-147
29	〃		184-185
30	〃		207-208
31	〃	$-CH_2COCH_3$	185-187
32	〃		199-200
33	〃		207-208
34	〃	$-COOC_2H_5$	205-207
35	〃	$-CH_2COOH$	186-188
36	〃	$-\underset{}{\overset{CH_3}{\overset{\vert}{C}}}HCOOH$	202-204

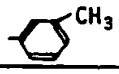
Compound No.	R^1	R^2	Melting point(°C)
37		$-CH_2COOC_2H_5$	153-154
38	〃	$-\overset{CH_3}{\underset{}{C}}HCOOC_2H_5$	oil
39	〃	$-CH_2CONH_2$	254-256
40	〃	$-CH_2CN$	219-220
41	〃	$-CH_2CH_2N(C_2H_5)_2$	239-240 (Hydrochloride)
42	〃		224-225 (Maleate)
43	〃		246-248 (Hydrochloride)
44	〃		137-139
45	〃		160-161
46	〃		155-156
47	〃	$-CH_2CH_2CH_2N(CH_3)_2$	143-144 (Hydrochloride)
48	〃		220-222 (Hydrochloride)
49	〃	$-CH_2CH_2NHCONH_2$	236-238
50	〃		161-162
51	〃		147-149
52		$-H$	315-316
53	〃	$-CH_3$	224-226
54	〃	$-C_2H_5$	214-216
55	〃	$-CH_2CH=CH_2$	173-175
56	〃	$-CH_2C\equiv CH$	173-175

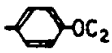
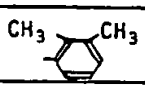
Compound No.	R^1	R^2	Melting point(°C)
57		$-CH_2CH_2OH$	209-211
58		-H	288-289
59	〃	$-C_2H_5$	222-224
60	〃	$-CH_2CH_2OH$	211-212
61		-H	above 315
62	〃	$-CH_3$	251-252
63	〃	$-C_2H_5$	192-193
64	〃	$-CH_2CH_2CH_3$	169-170
65	〃	$-CH_2CH=CH_2$	172-173
66	〃	$-CH_2C\equiv CH$	239-240
67	〃	$-CH_2CH_2Cl$	192-194
68	〃	$-CH_2CH_2OH$	227-228
69	〃	$-CH_2CH_2CH_2OH$	169-170
70	〃	$-CH_2CH_2OCOCH_3$	192-193
71	〃	$-CH_2OCH_3$	150-152
72	〃	$-CH_2OC_2H_5$	160-161
73	〃	$-CH_2CH_2OC_2H_5$	157-158
74	〃	$-CH_2COOC_2H_5$	194-195
75		-H	270-271
76	〃	$-CH_3$	244-245

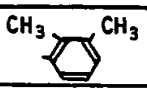
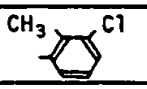
Compound No.	R1	R2	Melting point(°C)
77		$-C_2H_5$	180-181
78	〃	$-CH_2CH=CH_2$	170-172
79	〃	$-CH_2C\equiv CH$	215-216
80	〃	$-CH_2CH_2OH$	187-188
81	〃	$-CH_2CH_2OCOCH_3$	166-167
82	〃	$-CH_2OCH_3$	152-153
83	〃	$-CH_2CH_2OC_2H_5$	179-180
84	〃	$-CH_2COOC_2H_5$	164-165
85		-H	above 315
86	〃	$-CH_3$	197-198
87	〃	$-C_2H_5$	164-165
88	〃	$-CH_2CH_2CH_3$	153-154
89	〃	$-CH<\begin{matrix}CH_3\\CH_3\end{matrix}$	132-133
90	〃	$-CH_2CH_2CH_2CH_3$	143-144
91	〃	$-CH_2CH=CH_2$	186-187
92	〃	$-CH_2C\equiv CH$	265-266
93	〃	$-CH_2CH_2Cl$	169-170
94	〃	$-CH_2CH_2OH$	213-214
95	〃	$-CH_2CH_2CH_2OH$	177-178
96	〃	$-CH_2CH_2OCOCH_3$	173-174

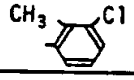
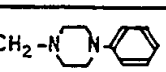
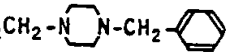
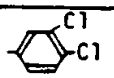
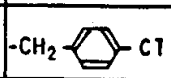
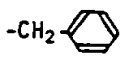
Compound No.	R^1	R^2	Melting point(°C)
97		$-CH_2OCH_3$	205-206
98	"	$-CH_2OC_2H_5$	169-170
99	"	$-CH_2CH_2OC_2H_5$	158-159
100	"		177-178
101	"		176-178
102	"		153-155
103	"	$-CH_2CH_2CH_2N<^{CH_3}_{CH_3}$	136-138
104		-H	292-294
105	"	$-C_2H_5$	188-189
106	"	$-CH_2CH_2CH_3$	195-196
107	"	$-CH_2CH_2CH_2CH_3$	126-127
108	"	$-CH_2CH=CH_2$	197-198
109	"	$-CH_2C\equiv CH$	226-227
110	"	$-CH_2CH_2Cl$	213-214
111	"	$-CH_2CH_2OH$	173-174
112	"	$-CH_2CH_2OCOCH_3$	174-175
113		-H	247-248
114	"	$-CH_3$	239-240
115	"	$-C_2H_5$	176-177
116	"	$-CH_2CH_2CH_3$	152-153

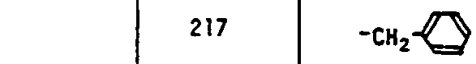
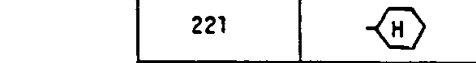
Compound No.	R^1	R^2	Melting point(°C)
117		$-CH<^{CH_3}_{CH_3}$	171-172
118	〃	$-CH_2CH=CH_2$	154-155
119	〃	$-CH_2C\equiv CH$	226-227
120	〃	$-CH_2CH_2Cl$	181-182
121	〃	$-CH_2CH_2OH$	176-177
122	〃	$-CH_2CH_2CH_2OH$	148-149
123	〃	$-CH_2CH_2OCOCH_3$	177-179
124	〃	$-CH_2CH_2OC_2H_5$	162-163
125	〃	$-CH_2COOC_2H_5$	131-132
126	〃	$-CH_2CON\square NCH_2CH_2OH$	104-105
127		-H	250-251
128	〃	$-CH_3$	259-260
129	〃	$-C_2H_5$	171-173
130	〃	$-CH_2CH_2CH_3$	151-152
131	〃	$-CH_2CH=CH_2$	141-142
132	〃	$-CH_2C\equiv CH$	185-186
133	〃	$-CH_2CH_2Cl$	168-170
134	〃	$-CH_2CH_2OH$	173-175
135	〃	$-CH_2CH_2CH_2OH$	153-154
136	〃	$-CH_2OCH_3$	144-146

Compound No.	R^1	R^2	Melting point(°C)
137		-H	274-275
138	〃	$-CH_3$	261-262
139	〃	$-CH_2CH_3$	177-178
140	〃	$-CH<^{CH_3}_{CH_3}$	167-168
141	〃	$-CH_2CH_2Cl$	192-193
142	〃	$-CH_2CH=CH_2$	161-162
143	〃	$-CH_2C\equiv CH$	183-184
144	〃	$-CH_2CH_2OH$	159-160
145	〃	$-CH_2CH_2CH_2OH$	154-155
146	〃	$-CH_2OCH_3$	168-169
147		-H	274-275
148	〃	$-C_2H_5$	178-180
149	〃	$-CH_2CH=CH_2$	184-186
150	〃	$-CH_2CH_2OH$	154-155
151		-H	260-261
152	〃	$-CH_3$	221-222
153	〃	$-C_2H_5$	182-183
154	〃	$-CH_2CH_2CH_3$	178-179
155	〃	$-CH<^{CH_3}_{CH_3}$	168-169
156	〃	$-CH_2CH_2CH_2CH_3$	158-159

Compound No.	R^1	R^2	Melting point(°C)
157		$-CH_2CH=CH_2$	162-164
158	〃	$-CH_2C\equiv CH$	201-202
159	〃	$-CH_2CH_2Cl$	183-184
160	〃	$-CH_2CH_2OH$	205-206
161	〃	$-CH_2CH_2OCOCH_3$	194-195
162	〃	$-CH_2OC_2H_5$	154-155
163	〃	$-CH_2CH_2OC_2H_5$	142-143
164	〃	$-CH_2COOC_2H_5$	172-173
165		-H	290-291
166	〃	$-CH_3$	207-208
167	〃	$-C_2H_5$	194-196
168	〃	$-CH_2CH=CH_2$	160-161
169	〃	$-CH_2CH_2OH$	171-172
170		-H	298-299
171	〃	$-C_2H_5$	190-191
172	〃	$-CH_2CH_2CH_3$	166-167
173	〃	$-CH<^{CH_3}_{CH_3}$	181-182
174	〃	$-CH_2CH=CH_2$	173-175
175	〃	$-CH_2C\equiv CH$	235-236
176	〃	$-CH_2CH_2Cl$	212-213

Compound No.	R^1	R^2	Melting point (°C)
177		$-CH_2CH_2OH$	193-195
178	"	$-CH_2CH_2OCOCH_3$	209-210
179	"	$-CH_2CH_2OC_2H_5$	167-168
180	"	$-CH_2COOC_2H_5$	196-197
181		$-H$	303-305
182	"	$-CH_3$	248-251
183	"	$-C_2H_5$	198-200
184	"	$-CH_2CH_2CH_3$	167-168
185	"	$-CH(CH_3)_2$	174-176
186	"	$-CH_2CH_2CH_2CH_3$	156-158
187	"	$-CH_2CH=CH_2$	162-163
188	"	$-CH_2C(CH_3)=CH_2$	164-166
189	"	$-CH_2CH=CHCl$	170-172
190	"	$-CH_2C\equiv CH$	177-178
191	"	$-CH_2CH_2Cl$	190-192
192	"	$-CH_2CH_2OH$	170-172
193	"	$-CH_2CH_2OCOCH_3$	226-228
194	"	$-CH_2OCH_3$	157-159
195	"	$-CH_2OC_2H_5$	159-160
196	"	$-CH_2CH_2OC_2H_5$	158-159

Compound No.	R^1	R^2	Melting point(°C)
197			130-132
198	〃		163-164
199	〃	$-CH_2COCH_3$	156-157
200	〃	$-CH_2COOC_2H_5$	198-199
201	〃	$-CH_2CN$	276-277
202	〃		172-173
203	〃		160-161
204		-H	278-279
205	〃	$-C_2H_5$	174-175
206	〃	$-CH_2CH=CH_2$	163-165
207	〃	$-CH_2CH_2Cl$	193-195
208	〃	$-CH_2CH_2OH$	193-194
209		-H	235-236
210	〃	$-CH_3$	179-180
211	〃	$-C_2H_5$	112-113
212	〃	$-CH_2CH_2OH$	122-123
213		-H	198-199
214	〃	$-CH_3$	149-150
215	〃	$-C_2H_5$	108-109
216	〃	$-CH<^{CH_3}_{CH_3}$	95-96

Compound No.	R^1	R^2	Melting point(°C)
217		$-CH_2CH=CH_2$	107-108
218	"	$-CH_2C\equiv CH$	148-149
219	"	$-CH_2CH_2Cl$	119-120
220	"	$-CH_2CH_2OH$	129-130
221		-H	223-224
222	"	$-C_2H_5$	134-135
223	"	$-CH_2CH_2CH_3$	131-132
224	"	$-CH<^{CH_3}_{CH_3}$	117-118
225	"	$-CH_2CH_2CH_2CH_3$	121-122
226	"	$-CH_2CH<^{CH_3}_{CH_3}$	123-124
227	"	$-CH_2CH=CH_2$	144-145
228	"	$-CH_2C\equiv CH$	162-164
229	"	$-CH_2CH_2Cl$	126-127
230	"	$-CH_2CH_2OH$	122-123
231	"	$-CH_2CH_2OCOCH_3$	128-130
232	"	$-CH_2OC_2H_5$	128-129
233	"	$-CH_2CH_2OC_2H_5$	82-83

Test Series:

With respect to numerous compounds of the present invention, the acute toxicity was tested to ensure their safety and further the central nervous depressive, anti-inflammatory and analgetic effects were tested to prove their excellent activities. The results of the tests are indicated in Table II. Each test was conducted in the following manner.

(1) Acute Toxicity

Each test compound suspended in 0.5% CMC-physiological saline was injected intraperitoneally to dd-strain male mice (16—24 g). A lethal dose was estimated from the death of animals 24 hours after administration.

(2) Central nervous system depressive effect.

Each test compound suspended in 0.5% CMC-physiological saline was injected intraperitoneally to dd-strain male mice (16—24 g). The disappearance of righting reflex was observed under noiseless circumstances.

The dose required for the disappearance of righting reflex is indicated with the following notation:

more than 1,000 (mg/kg):— 100—30 (mg/kg):++
1000—300 (mg/kg):± less than 30 (mg/kg):+++
300—100 (mg/kg):+

(3) Anti-inflammatory effect.

A group of five Wistar-strain male rats (100—150 g) were orally administered with each test compound suspended in 0.5% CMC-physiological saline. After 30 min. 0.5%—1.0% carrageenin suspended in the water for injection was injected subcutaneously into a hind paw. After 3 hours the carrageenin edema was measured by volume and the inhibition percentage was determined with respect to the results for animals. The inhibition percentages are indicated with the following notation:

less than 15%:± 31—45%:++
16—30%:+ more than 46%+++

(4) Analgetic Effect.

Each test compound suspended in 0.5% CMC-physiological saline was orally administered to dd-strain male mice (18—20 g). After one hour 0.6% acetic acid solution was intraperitoneally injected at the rate of 0.1 ml/10g. The writhing syndrome was observed for 10 min. from 30 min. after administration, and the inhibition percentage compared with a control animal was determined.

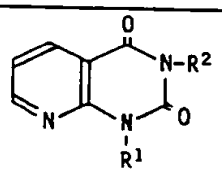
The inhibition percentages are shown with the following notation:

Less than 25%:± 51—75%:++
26—25%:+ more than 76%:+++

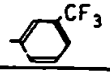
Table II

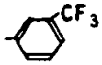
Anti-inflammatory, Analgetic and Central Nervous System Depressive Effects, and Acute Toxicity of the Object Compounds of General Formula [A]

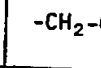
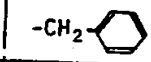
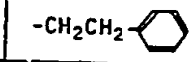
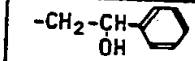
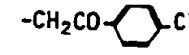
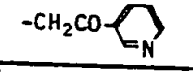
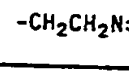
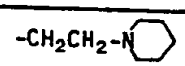
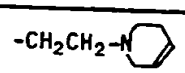
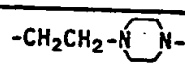
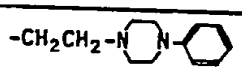
Standard	anti-inflammatory effect dose(mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
phenylbutazone	++ ++ +	±	±	300-1000
flufenamic acid	++ + ±	+	-	300-1000
aminopyrine	+ ± ±	++	/	100-300
methaqualone	/ / /	+	+++	300-1000
diazepam	++ + +	+	++	300-1000

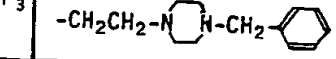
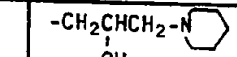
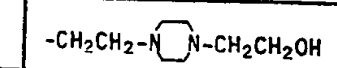
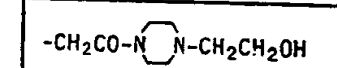
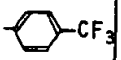
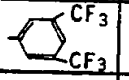


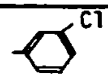
[A]

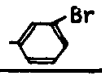
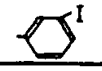
R^1	R^2	anti-inflammatory effect dose(mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	-H	+ ± /	±	-	> 1000
〃	$-CH_3$	++ + +	+++	±	> 1000
〃	$-C_2H_5$	+++ +++ +++	+++	+++	> 1000
〃	$-CH_2CH_2CH_3$	++ + +	++	-	> 1000
〃	$-CH\langle^{CH_3}_{CH_3}$	+++ ++ ++	+	±	> 1000

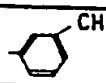
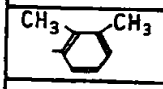
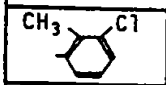
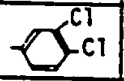
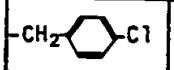
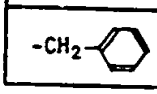
R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	$-CH_2CH_2CH_2CH_3$	± / /	+	-	>1000
〃	$-CH_2CH=CH_2$	++ ++ ++	++	++	>1000
〃	$-CH_2\overset{CH_3}{\overset{\vert}{C}}=CH_2$	++ / /	++	-	>1000
〃	$-CH_2CH=CHCl$	++ + +	+++	-	>1000
〃	$-CH_2C\equiv CH$	++ ++ +	±	++	>1000
〃	$-CH_2CH_2Cl$	++ ++ ++	++	-	>1000
〃	$-CH_2CH_2Br$	++ ++ +	++	-	>1000
〃	$-CH_2CH_2CH_2Cl$	± / /	++	-	>1000
〃	$-CH_2CH_2OH$	++ ++ ++	+++	+++	300-1000
〃	$-CH_2CH_2CH_2OH$	++ ++ ++	++	++	300-1000
〃	$-CH_2\underset{\vert}{\overset{\vert}{C}}H-CH_3$ (OH)	++ ++ ++	++	++	>1000
〃	$-CH_2\underset{\vert}{\overset{\vert}{C}}H-CH_2OH$ (OH)	++ ++ /	+++	+	>1000
〃	$-CH_2\underset{\vert}{\overset{\vert}{C}}H-CH_2Cl$ (OH)	/ / /	+	±	>1000
〃	$-CH_2CH_2OCOCH_3$	++ ++ ++	++	+	>1000
〃	$-CH_2OCH_3$	++ + ±	++	++	300-1000
〃	$-CH_2OC_2H_5$	+ + ±	+	++	>1000
〃	$-CH_2CH_2OC_2H_5$	++ ++ ++	+	+	>1000

R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	$-CH_2CH_2OCH=CH_2$	++ ++ /	±	-	> 1000
〃	$-CH_2CH_2OCH_2CH_2OH$	+++ +++ ++	+++	++	300-1000
〃	$-CH_2\underset{Cl}{CH}OC_2H_5$	+ / /	++	-	> 1000
〃		++ ++ ++	+	-	> 1000
〃		+++ ++ +	±	-	> 1000
〃		± / /	+	-	> 1000
〃		± / /	/	-	> 1000
〃	$-CH_2COCH_3$	± / /	±	-	> 1000
〃		± / /	++	-	> 1000
〃		++ + +	/	-	> 1000
〃	$-CH_2COOH$	± / /	±	-	> 1000
〃	$-CH_2COOC_2H_5$	± / /	+	-	> 1000
〃		++ ± /	+	+	100-300
〃		++ + /	++	+	100-300
〃		+ + /	/	±	300-1000
〃		++ + +	/	±	300-1000
〃		++ ++ /	/	-	> 1000

R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
		++ ± /	+	-	>1000
〃	$-CH_2CH_2CH_2N<^{CH_3}_{CH_3}$	+++ ++ ++	/	+	100-300
〃		++ ++ ±	±	-	100-300
〃	$-CH_2CH_2NHCONH_2$	+ ± /	+	-	>1000
〃		± / /	+	-	300-1000
〃		++ + +	/	-	>1000
	$-C_2H_5$	+ / /	+	-	>1000
〃	$-CH_2CH_2OH$	+ / /	+	-	>1000
	$-C_2H_5$	± / /	±	-	>1000
〃	$-CH_2CH_2OH$	+ / /	±	-	>1000
	$-C_2H_5$	+++ +++ +++	+++	++	>1000
〃	$-CH_2CH_2CH_3$	+++ +++ +++	+	±	300-1000
〃	$-CH_2CH=CH_2$	+++ +++ +++	+	-	>1000
〃	$-CH_2C\equiv CH$	+++ +++ +++	++	±	300-1000
〃	$-CH_2CH_2Cl$	+++ +++ +++	+	±	>1000
〃	$-CH_2CH_2OH$	+ ± /	+++	-	>1000
〃	$-CH_2CH_2CH_2OH$	+++ / /	++	±	300-1000

R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	$-CH_3$	/ / /	++	-	>1000
〃	$-C_2H_5$	++ ± /	+	+	>1000
〃	$-CH_2CH=CH_2$	/ / /	++	-	>1000
〃	$-CH_2CH_2OH$	± / /	++	+	100-300
	$-C_2H_5$	+++ +++ +++	+++	++	300-1000
〃	$-CH_2CH=CH_2$	+++ +++ +++	+	-	>1000
〃	$-CH_2C\equiv CH$	++ / /	+	-	>1000
〃	$-CH_2CH_2Cl$	++ / /	+	±	>1000
〃	$-CH_2CH_2OH$	+ + ±	+++	±	>1000
〃	$-CH_2CH_2CH_2OH$	+++ +++ ++	++	±	300-1000
	$-C_2H_5$	/ / /	+	-	>1000
〃	$-CH_2CH_2OH$	/ / /	+	++	300-1000
	$-CH_3$	+++ +++ +++	+++	±	>1000
〃	$-C_2H_5$	+++ +++ +++	++	+	>1000
〃	$-CH_2CH_2CH_3$	+++ +++ +++	+++	+	300-1000
〃	$-CH<^{CH_3}_{CH_3}$	+++ +++ +++	++	++	>1000
〃	$-CH_2CH=CH_2$	+++ +++ ++	++	+	>1000

R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	$-CH_2C\equiv CH$	+++ +++ +++	++	-	>1000
〃	$-CH_2CH_2Cl$	+++ +++ +++	+++	+	300-1000
〃	$-CH_2CH_2OH$	+ + ±	++	-	>1000
〃	$-CH_2CH_2CH_2OH$	+++ +++ +++	++	±	300-1000
〃	$-CH_2CH_2OC_2H_5$	++ ++ +	++	+	>1000
	$-C_2H_5$	+++ +++ ++	+++	++	>1000
〃	$-CH_2CH_2CH_3$	+++ +++ +++	++	±	>1000
〃	$-CH_2CH=CH_2$	+++ +++ ++	++	-	>1000
〃	$-CH_2C\equiv CH$	+++ +++ +++	+++	-	>1000
〃	$-CH_2CH_2Cl$	+++ +++ +++	+++	-	>1000
〃	$-CH_2CH_2OH$	+++ +++ +++	+++	++	>1000
〃	$-CH_2CH_2CH_2OH$	+++ +++ +++	++	±	300-1000
〃	$-CH_2OCH_3$	+++ +++ ++	+++	-	>1000
	$-CH_2CH_3$	+++ +++ +++	+++	+	>1000
〃	$-CH_2CH_2Cl$	/ / /	±	±	>1000
〃	$-CH_2CH_2CH_2OH$	/ / /	++	-	>1000
〃	$-CH_2CH=CH_2$	/ / /	+++	±	>1000

R^1	R^2	anti-inflammatory effect dose (mg/kg) 100 50 20	analgetic effect (100mg/kg)	C N S depressive effect	acute toxicity (mg/kg)
	$-CH_2CH=CH_2$	+++ +++ +++	+	+	>1000
〃	$-CH_2C\equiv CH$	+++ +++ +++	++	-	>1000
〃	$-CH_2CH_2Cl$	+++ ++ /	-	-	>1000
〃	$-CH_2CH_2OH$	+ / /	+	±	>1000
	$-C_2H_5$	± / /	+	-	>1000
〃	$-CH_2CH=CH_2$	/ / /	-	-	>1000
〃	$-CH_2C\equiv CH$	/ / /	±	-	>1000
〃	$-CH_2CH_2Cl$	/ / /	+	-	>1000
〃	$-CH_2CH_2OH$	± / /	+	±	>1000
	$-C_2H_5$	++ + +	+	-	>1000
	$-C_2H_5$	+++ +++ +++	++	-	>1000
〃	$-CH_2CH=CH_2$	± / /	++	-	>1000
〃	$-CH_2CH_2Cl$	+++ ++ ±	++	-	>1000
〃	$-CH_2CH_2OH$	± / /	+++	±	300-1000
	$-C_2H_5$	+ + ±	-	-	>1000
〃	$-CH_2CH_2OH$	++ + ±	-	-	>1000
	$-C_2H_5$	/ / /	++	-	>1000

Example 1.

To a mixture of 3.1 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]-pyrimidine-2,4(1H,3H)-dione and 40 ml of dried dimethylformamide was added 0.7 g of 50% sodium hydride, and the mixture was stirred for one hour at room temperature. Then 0.6 g of methyl iodide was further added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure, and to the residue was added water. The crystals produced were recrystallized from methanol 2.7 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 221.5—222°C
Ultimate analysis value $C_{15}H_{10}F_3N_3O_2$
Theoretical values C:56.08, H:3.14, N:13.08
Found values C:55.93, H:2.92, N:13.02

Example 2.

Sodium ethoxide was prepared from 0.6 g of metallic sodium and 15 ml of ethyl alcohol. To this was added a solution obtained by dissolving 6.2 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 20 cc of dried dimethylformamide. Then 5.5 g of ethyl iodide was added and the mixture was stirred for 1.5 hours at room temperature. Water was further added, the crystals produced were filtered and dried and upon recrystallization from methanol, 5.3 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-ethylpyrido[2,3-d]pyridimidine-2,4(1H,3H)-dione were obtained.

Melting point 160—161°C
Ultimate analysis value $C_{16}H_{12}F_3N_3O_2$
Theoretical values C:57.31, H:3.61, N:12.53
Found values C:57.64, H:3.65, N:12.30

Example 3.

To a mixture of 2.7 g of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 40 ml of dried dimethylformamide was added 0.6 g of 50% sodium hydride and the mixture was stirred for one hour. 3.3 g of 2-bromoethylacetate was further added and the mixture was allowed to react for 2 hours at room temperature. The solvent was then distilled off under reduced pressure and to the residue was added water. The crystals produced were filtered and dried, and upon recrystallization from methanol, 2.6 g of colorless prisms of 1-(m-chlorophenyl)-3-(2-acetoxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 177—179°C
Ultimate analysis value $C_{17}H_{14}ClN_3O_4$
Theoretical values C:56.75, H:3.92, N:11.68
Found values C:56.92, H:3.90, N:11.73

Example 4.

To a solution of 2.9 g of 1-(2-methyl-3-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 20 ml of dried dimethylformamide was added 0.53 g of 50% sodium hydride and the mixture was stirred for 30 minutes. 2.1 g of n-butyl iodide was then added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added water and the crystals produced were filtered. Upon recrystallization from ethylether and petroleum benzine, 2.8 g of colorless prisms of 1-(2-methyl-3-chlorophenyl)-3-n-butylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 156—158°C
Ultimate analysis value $C_{18}H_{18}ClO_2N_3$
Theoretical values C:62.88, H:5.28, N:12.22
Found values C:62.76, H:5.15, N:12.13

Example 5.

To a solution of 2.5 g of 1-(o-tolyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 40 ml of dried dimethylformamide was added 0.7 g of 50% sodium hydride and the mixture was stirred for one hour. Then 2.4 g of allyl iodide was added and the mixture was allowed to react for 30 minutes at room temperature. The solvent was distilled off under reduced pressure, and to the residue was added water. The

crystals produced were filtered, and, upon recrystallization from methanol, 2.4 g of colorless prisms of 1-(o-tolyl)-3-allylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 185—186°C
Ultimate analysis value $C_{17}H_{15}N_3O_2$
Theoretical values C:69.61, H:5.15, N:14.33
Found values C:69.53, H:5.28, N:14.21

Example 6.

To a solution of 2.8 g of 1-(p-ethoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 40 ml of dried dimethylformamide was added 0.53 g of 50% sodium hydride and the mixture was stirred for one hour. 2.5 g of ethylenebromohydrin were then added and the mixture was allowed to react for 30 minutes at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added water and the crystals produced were filtered. Upon recrystallization from methanol, 3.1 g of colorless needles of 1-(p-ethoxyphenyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 171—172°C
Ultimate analysis value $C_{17}H_{17}N_3O_4$
Theoretical values C:62.37, H:5.24, N:12.84
Found values C:62.34, H:5.15, N:12.91.

Example 7.

To a solution of 2.6 g of 1-(m-fluorophenyl)pyrido[2,3-d]pyrimidine-2,3(1H,3H)-dione and 30 ml dried dimethylformamide was added 0.6 g of 50 % sodium hydride and the mixture was stirred for 30 minutes. Then 1.9 g of methyl iodide were added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure, water was added to the residue, and the mixture was extracted with ether. Evaporation of the solvent gave 2.5 g of colorless prisms of 1-(m-fluorophenyl)-3-methylpyrido[2,3-d]pyrimidine-2,3(1H,3H)-dione.

Melting point 197—198°C
Ultimate analysis value $C_{14}H_{10}FN_3O_2$
Theoretical values C:61.99, H:3.72, N:15.49
Found values C:61.83, H:3.81, N:15.38

Example 8.

To a solution of 15 ml of ethyl alcohol and 0.28 g of metallic sodium was added a solution of 3.1 g of 1-(0-fluorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 15 ml of dimethylformamide, and the mixture was stirred for 30 minutes. Then 2.2 g of ethylbromide was added to the mixture, and the whole was stirred for 2 hours at room temperature. Water was added to the reaction mixture and the crystals produced were recrystallized from methanol to give 2.9 g of colorless prisms of 1-(o-fluorophenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 180—181°C
Ultimate analysis value $C_{15}H_{12}FN_3O_2$
Theoretical values C:63.15, H:4.25, N:14.73
Found values C:63.23, H:4.18, N:14.62

Example 9.

To a solution of 2.4 g of 1-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 30 ml of dimethylformamide was added 0.5 g of sodium amide, and the whole was stirred for one hour. 1.6 g of chlorodimethylether was added to the mixture which was then allowed to stand for 2 hours. Then the solvent was evaporated under reduced pressure, and to the residue was added water. The crystals produced were recrystallized from methanol to give 2.0 g of colorless prisms of 1-phenyl-3-methoxymethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 150—152°C
Ultimate analysis value $C_{15}H_{13}N_3O_3$
Theoretical values C:63.59, H:4.63, N:14.83
Found values C:63.48, H:4.72, N:14.78

Example 10.

To a solution of 0.95 g of 1-(p-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 25 ml dried dimethylformamide was added 0.17 f of 50% sodium hydride, and the mixture was stirred for 30 minutes. Then 1.3 g of O-(p-tosyl)ethyleneglycol was added, and the mixture was stirred for one hour at room temperature, and then allowed to react for 30 minutes at 60°C. The solvent was distilled off under reduced pressure and to the residue was added water. Upon recrystallization from methanol, 0.85 g of colorless prisms of 1-(p-trifluoromethylphenyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 209—211°C
Ultimate analysis value $C_{16}H_{12}F_3N_3O_3$
Theoretical values C:54.70, H:3.44, N:11.96
Found values C:54.52, H:3.28, N:12.10

Example 11.

To a solution of 2.7 g of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 30 ml of dried xylene was added 0.58 g of sodium amide, and the mixture was stirred for one hour. To the resulting solution was added 3.7 g of benzenesulfonyl ethyl ester, and the whole was reacted for 2 hours at 80°C. The solvent was then distilled off under reduced pressure, and upon recrystallization from methanol, 2.6 g of 1-(m-chlorophenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 176—177°C
Ultimate analysis value $C_{15}H_{12}ClN_3O_2$
Theoretical values C:59.71, H:4.01, N:13.93
Found values C:59.74, H:3.91, N:13.99

Example 12.

To a solution of 3.1 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 20 ml of dimethylformamide was added 0.58 g of 50% sodium hydride, and the mixture was stirred for 30 minutes at room temperature. Then 1.8 g of 3-chloro-2-methyl-1-propene was added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added water and the crystals produced were filtered. Upon recrystallization from methanol, 2.9 g of colorless plates of 1-(m-trifluoromethylphenyl) - 3 - (2 - methylallyl)pyrido[2,3 - d]pyrimidine - 2,4-(1H,3H)-dione were obtained.

Melting point 130—131°C
Ultimate analysis value $C_{18}H_{14}F_3N_3O_2$
Theoretical values C:59.83, H:3.91, N:11.63
Found values C:59.79, H:3.87, N:11.69

Example 13.

To a solution of 1-(p-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 20 ml of dimethylformamide was added 0.58 g of 50% sodium hydride, and the mixture was stirred for 30 minutes. Then 3.1 g of ethyliodide were added and the mixture was stirred for one hour at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added water, and the crystals produced were filtered. Upon recrystallization from methanol, 3.0 g of colorless prisms of 1-(p-trifluoromethylphenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 214—215°C
Ultimate analysis value $C_{16}H_{12}F_3N_3O_2$
Theoretical values C:57.31, H:3.61, N:12.53
Found values C:57.58, H:3.71, N:12.61

Example 14.

To a solution of 3.1 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 25 ml of dimethylformamide was added 0.72 g of sodium hydride and the mixture was stirred for 30 minutes. 5.1 g of ethyl O-(p-tosyl)glycolate were then added and the whole was reacted for one hour at 80°C. The solvent was then distilled off under reduced pressure, and upon recrystallization of the residue from methanol, 2.8 g of colorless prisms of 1-(m-

trifluoromethylphenyl) - 3 - ethoxycarbonylmethylpyrido[2,3 - d]pyridmidine - 2,4(1H,3H)-dione were obtained.

Melting point 153—154°C
Ultimate analysis value $C_{18}H_{14}F_3N_3O_4$
Theoretical values C:54.94, H:3.59, N:10.68
Found values C:54.82, H:3.47, N:10.52.

Example 15.

To a solution of 0.2 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 15 ml of dried dimethylformamide was added 0.05 g of 50% sodium hydride, and the mixture was stirred for one hour at room temperature. To the mixture was added a solution obtained by dissolving 0.24 g of chloroacetoamide in 5 ml of dried dimethylformamide, and the mixture was stirred for 2 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, and the crystals produced were filtered and dried. Upon recrystallization from methanol, 0.18 g of colorless prisms of 1-(m - trifluoromethylphenyl) - 3 carbamoylmethylpyrido[2,3 - d]pyrimidine - 2,4(1H,3H)-dione was obtained.

Melting point 254—256°C
Ultimate analysis value $C_{16}H_{11}F_3N_4O_3$
Theoretical values C:52.77, H:3.04, N:15.38
Found values C:52.85, H:3.19, N:15.54

Example 16.

To a solution of 3.1 g of 1-(m-trifluoromethylphenyl)pyrido [2,3-d]pyrimidine-2,4(1H,3H)-dione and 30 ml of dried dimethylformamide was added 0.72 g of 50% sodium hydride, and the mixture was stirred for one hour. Then 2.5 g of ethyl chloroacetate was added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water and the crystals produced were recrystallized from methanol. 3.2 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-ethoxycarbonylmethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 153—154°C
Ultimate analysis value $C_{18}H_{14}F_3N_3O_4$
Theoretical values C:54.97, H:3.59, N:10.68
Found values C:55.06, H:3.41, N:10.63

Example 17.

To a solution of 12 ml of acetic acid and 40 ml of concentrated hydrochloric acid was added 0.6 g of 1-(m-trifluoromethylphenyl)-3-ethoxycarbonylmethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione, and the mixture was reacted for 20 hours. The solvent was then distilled off under reduced pressure, the residue was crystallized from methanol and water, and 0.46 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-carboxymethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

Melting point 186—188°C
Ultimate analysis value $C_{16}H_{10}F_3N_3O_4$
Theoretical values C:52.61, H:2.76, N:11.51
Found values C:52.41, H:2.82, N:11.35

Example 18.

To a solution of 2.7 g of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 30 ml of dried dimethylformamide was added 0.72 g of 50% sodium hydride, and the mixture was stirred for one hour at room temperature. Then 2.5 g of ethyl chloroacetate was further added and the mixture was reacted for 1.5 hours at room temperature. The solvent was then distilled off under pressure; to the residue was added water and upon recrystallization from methanol, 3.1 g of colorless prisms of 1-(m-chlorophenyl)-3-ethoxycarbonylmethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 131—132°C
Ultimate analysis value $C_{17}H_{14}ClN_3O_4$
Theoretical values C:56.75, H:3.92, N:11.68
Found values C:56.53, H:3.81, N:11.56

Example 19.

To a solution of 1.0 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 20 ml dried dimethylformamide was added 0.24 g of 50% sodium hydride, and the mixture was stirred for one hour. Then 1.8 g of ethyl α-bromopropionate was added and the mixture was allowed to react for one hour at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, and the mixture was extracted with ether. After evaporation of ether, 1.0 g of light yellow oil 1-(trifluoromethylphenyl)-3-(1-ethoxycarbonylethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

IR : $\nu_{C=O}^{liquid}$ 1750, 1725 and 1680 cm^{-1}

Mass: parent ion 395.

Example 20.

To a solution of 20 ml acetic acid and 40 ml concentrated hydrochloric acid was added 1-(m-trifluoromethylphenyl)-3-(1-ethoxycarbonylethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione, and the mixture was refluxed for 15 hours. The solvent was then distilled off under reduced pressure, the residue obtained was recrystallized from methanol and water, and 0.72 g of colorless prisms of 1-(m-trifluoromethylphenyl) - 3 - (1 - carboxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

Melting point 202—204°C
Ultimate analysis value $C_{17}H_{12}F_3N_3O_4$
Theoretical values C:53.83, H:3.19, N:11.08
Found values C:53.62, H:3.05, N:11.21

Example 21.

To a solution of 0.2 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 20 ml dried dimethylformamide was added 0.05 g of 50% sodium hydride, and the mixture was stirred for 0.5 hour. Then 0.1 g of chloroacetonitrile was added and the mixture was allowed to react for 2 hours at room temperature. The solvent was then distilled off under reduced pressure, and to the residue was added water. The crystals produced were filtered and dried, and upon recrystallization from methanol 0.2 g of colorless prisms of 1-(m-trifluoromethylphenyl) - 3 - cyanomethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

Melting point 219—220°C
Ultimate analysis value $C_{16}H_9F_3N_4O_2$
Theoretical values C:55.51, H:2.62, N:16.18
Found values C:55.23, H:2.92, N:16.42

Example 22.

To a solution of 2.7 g of 1-(2,3-xylyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 30 ml dried dimethylformamide was added 0.7 g of 50% sodium hydride, and the mixture was stirred for 0.5 hour. Then 3.1 g of ethyl chloroacetate was further added and the mixture was reacted for 1.5 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water and the crystals produced were recrystallized from methanol. 3.2 g of colorless prisms of 1-(2,3-xylyl)3-ethoxycarbonylmethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 196—197°C
Ultimate analysis value $C_{19}H_{19}N_3O_4$
Theoretical values C:64.58, H:5.42, N:11.89
Found values C:64.61, H:5.38, N:11.78

Example 23.

A mixture of 0.5 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione, 1 g of dimethylsulfate and 30 ml of acetone was refluxed for 12 hours. The residue was neutralized with 10% sodium carbonate solution under cooling, and the crystals precipitated were filtered. Upon recrystallization from methanol, 0.45 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

Melting point 221—222°C
Ultimate analysis value $C_{15}H_{10}F_3N_3O_2$
Theoretical values C:56.08, H:3.14, N:13.08
Found values C:56.13, H:3.21, N:13.17

Example 24.

To a solution of 1 g of 1-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 20 ml of dimethylformamide was added 0.25 g of 50% sodium hydride, and the mixture was reacted for 30 minutes with stirring. Then 1.2 g of diethyl sulfate was further added and the mixture was allowed to react for one hour at room temperature. The solvent was distilled off under reduced pressure, and the residue was neutralized with 10% sodium carbonate solution under cooling. The crystals produced were recrystallized from methanol to give 0.8 g of colorless needles of 1-phenyl-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 192—193°C
Ultimate analysis value $C_{15}H_{13}N_3O_2$
Theoretical values C:67.40, H:4.90, N:15.72
Found values C:67.25, H:4.94, N:15.63

Example 25

A mixture of 2.7 g of 1-(m-chlorophhenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 1,18 g of dimethyl oxalate was heated for 70 hours at 210—220°C in a sealed tube. To the mixture was added 30 ml of chloroform, the insoluble material was filtered off, and the filtrate was concentrated to dryness under reduced pressure. Upon recrystallization from methanol, 1.5 g of colorless prisms of 1-(m-chlorophenyl)-3-methyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 239 –240°C
Ultimate analysis value $C_{14}H_{10}ClN_3O_2$
Theoretical values C:58.44, H:3.50, N:14.61
Found values C:58.48, H:3.52, N:14.58

Example 26.

To 30 ml of benzene were successively added 3.1 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione, 0.48 g of sodium hydride and 12 g of diethyl carbonate. The mixture was heated in an autoclave at 200°C for 4 hours and then concentrated under reduced pressure. To the residue was added 50 ml of chloroform and the insoluble material was filtered off. The solvent was distilled off to give crystals. Upon recrystallization from methanol, 2.8 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 161—162°C
Ultimate analysis value $C_{16}H_{12}F_3N_3O_2$
Theoretical values C:57.31, H:3.61, N:12.53
Found values C:57.45, H:3.92, N:12.62

Example 27.

To a solution of 2.7 g of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 20 ml dimethylformamide were added 1.8 g of ethylene carbonate, and the mixture was reacted for 1.5 hours at 145—155°C on an oil bath. The solvent was evaporated off under reduced pressure, and to the residue was added ice water. The crystals produced were filtered, and upon recrystallization from the mixed solvent of ether and petroleum ether, 2.5 g of colorless prisms of 1-(m - chlorophenyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine - 2,4(1H,3H) - dione were obtained.

Melting point 176—177°C
Ultimate analysis value $C_{15}H_{12}N_3O_3Cl$
Theoretical values C:56.70, H:3.81, N:13.23
Found values C:56.53, H:3.37, N:13.31

Example 28.

To a solution of 1 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 10 ml dimethylformamide were added 1.7 g of propylene carbonate, and the mixture was refluxed for 3 hours. The solvent was evaporated off under reduced pressure, and the residue was extracted with ether. Evaporation of the solvent from the ether extracts gave 0.82 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-(2-hydroxypropyl)pyrido[2,3-d]pyrimidine - 2,4(1H,3H) - dione.

Melting point 167—169°C
Ultimate analysis value $C_{17}H_{14}N_3O_3F_3$
Theoretical values C:55.89, H:3.86, N:11.50
Found values C:55.73, H:3.76, N:11.45

Example 29.

To a solution of 1.3 g of 1-(2,3-xylyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 15 ml of dimethylformamide was added 0.84 of ethylene carbonate, and the mixture was allowed to react for one hour at 150—155°C. To the residue was added water and the crystals obtained were filtered. Upon recrystallization from the mixed solvent of methanol and water, 1.1 g of colorless prisms of 1-(2,3-xylyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 193—195°C
Ultimate analysis value $C_{17}H_{17}N_3O_3$
Theoretical values C:65.58, H:5.50, N:13.50
Found values C:65.42, H:5.61, N:13.32

Example 30.

To a solution of 2 g of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 20 ml of dimethylformamide were added 8 ml of glycol sulfide and 8 ml of pyridine, and the mixture was allowed to stand for 40 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was extracted with ether. The ether extracts were washed with water, dried with sodium sulfate and concentrated. The residue was allowed to stand at room temperature to yield 1.9 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 142—143°C
Ultimate analysis value $C_{16}H_{12}N_3O_3F_3$
Theoretical values C:54.70, H:3.44, N:11.96
Found values C:56.62, H:3.43, N:11.87

Example 31.

To a solution of 1 g of 1-(m-trifluoromethylphenyl)pyrdio[2,3-d]pyrimidine-2,4(1H,3H)-dione and 15 ml of dimethylformamide were added 4 ml of pyridine and 4 ml of propyleneoxide, and the mixture was stirred for 24 hours at room temperature. The solvent was distilled off under reduced pressure and to the residue was added water. The oily product obtained was extracted with ether. After concentration of the extracts, 0.92 of colorless prisms of 1-(m-trifluoromethylphenyl)-3-(2-hydroxypropyl)pyrido[2,3-d]pyrimidine - 2,4(1H,3H)-dione was obtained.

Melting point 167—169°C
Ultimate analysis value $C_{17}H_{14}F_3N_3O_3$
Theoretical values C:55.98, H:3.86, N:11.50
Found values C:55.73, H:3.78, N:11.43

Example 32.

To a solution of 1 g of 1-(2,3-xylyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione and 15 ml of dimethylformamide were added 4 ml of pyridine and 4 ml of ethyleneoxide, and the mixture was stirred for 24 hours at room temperature. The solvent was distilled off under reduced pressure, and to the residue was added water. The crystals produced were filtered, and upon recrystallization from methanol, 0.8 g of colorless prisms of 1-(2,3-xylyl)-3-(2-hydroxyethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione was obtained.

Melting point 193—195°C
Ultimate analysis value $C_{17}H_{17}N_3O_3$
Theoretical values C:65.58, H:5.50, N:13.50
Found values C:65.37, H:5.52, N:13.47

Example 33

To a solution of 3.1 g of 1-(m-trifluoromethyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione in 30 ml of methanol and 20 ml of chloroform were added dropwise 50 ml of diazomethane-ether solution (about 2%) with stirring under ice-cooling, the mixture was allowed to stand for 5 hours at room temperature and was then heated for one hour at 55—60°C. After reaction, the solvent was distilled off and 3.1 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 222—223°C
Ultimate analysis value $C_{15}H_{10}F_3N_3O_2$
Theoretical values C:56.08, H:3.14, N:13.08
Found values C:56.12, H:3.10, N:13.06

Example 34.

To a solution of 50 ml of ethyl alcohol and 1.7 g of metallic sodium were added 3.7 g of 2-(m-chloroanilino)nicotinamide and 8.7 g of diethyl carbonate. The mixture was refluxed for 1.5 hours, neutralized with acetic acid and water was added. The crystals produced were filtered, and upon recrystallization from methanol, 3.6 g of colorless prisms of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 247—248°C
Ultimate analysis value $C_{13}H_8O_2N_3Cl$
Theoretical values C:57.05, H:2.95, N:15.36
Found values C:57.32, H:2.97, N:15.21

Example 35.

To a solution of 50 ml of ethyl alcohol and 2.3 g of metallic sodium were added 3.6 g of 2-anilinonicotinamide and 12.0 g of diethyl carbonate. The mixture was allowed to stand for one hour at room temperature and was now neutralized with 10% hydrochloric acid. The crystals produced were recrystallized from dimethylformamide, and 3.4 g of colorless needles of 1-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point above 315°C
Ultimate analysis value $C_{13}H_9O_2N_3$
Theoretical values C:65.25, H:3.79, N:17.57
Found values C:65.12, H:3.71, N:17.45
IR: $\nu_{C=O}^{KBr}$ 1718, 1692 cm^{-1}
Mass: parent ion 239

Example 36.

To a solution of 3.2 g of 2-(2-methyl-3-chloroanilino)nicotin-n-butylamide in 25 ml of dried tetrahydrofuran were added 0.6 g of sodium hydride and 5.9 g of diethyl carbonate and the mixture was refluxed for 12 hours. The solvent was then distilled off under reduced pressure and to the residue was added water. The crystals produced were filtered, and upon recrystallization from the mixed solvents of ether and petroleum benzine, 2.9 g of colorless prisms of 1-(2-methyl-3-chlorophenyl)-3n-buthylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 156—158°C
Ultimate analysis value $C_{18}H_{18}ClN_3O_2$
Theoretical values C:62.88, H:5.28, N:12.21
Found values C:62.75, H:5.23, N:12.16

Example 37.

To a solution of 2.3 g of 2-anilinonicotinmethylamide in 18 ml of dried diglyme were added 0.6 g of 50% sodium hydride and 5.9 g of diethyl carbonate, and the mixture was refluxed for 12 hours. The solvent was distilled off under reduced pressure and to the residue was added water. The crystals produced were filtered, and upon recrystallization from methanol, 1.8 g of colorless prisms of 1-phenyl-3-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione were obtained.

Melting point 251—252°C
Ultimate analysis value $C_{14}H_{11}N_3O_2$
Theoretical values C:66.40, H:4.38, N:16.59
Found values C:66.38, H:4.29, N:16.43

Example 38.

To a solution of 3.1 g of 2-(m-trifluoromethylanilino)nicotinethylamide and 50 ml of tetrahydrofuran were added 1 g of 50% sodium hydride and 4.9 g of 1,1'-carbonyldiimidazole. Then the mixture was stirred for one hour at room temperature and refluxed for 5 hours. The solvent was distilled off under reduced pressure and to the residue was added ice water. The crystals produced were recrystallized from methanol to give 2.1 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-ethyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 163—164°C
Ultimate analysis value $C_{16}H_{12}F_3N_3O_2$
Theoretical values C:57.31, H:3.61, N:12.83
Found values C:57.45, H:3.82, N:12.62

Example 39.

To a solution of 2.8 g of 2-(m-trifluoromethylanilino)nicotinamide in 25 ml of tetrahydrofuran was added 0.48 g of 50% sodium hydride. The mixture was stirred for 15 minutes at room temperature, and then 5.4 g of ethyl chlorocarbonate were added dropwise under cooling. The solution was allowed to stand for one hour and refluxed for 10 hours. The solvent was distilled off under reduced pressure, water was added to the residue and the crystals obtained were recrystallized from the mixed solvent of dimethylformamide and methanol to yield 1.5 g of colorless prisms of 1-(m-trifluoromethylphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 259—260°C
Ultimate analysis value $C_{14}H_8F_3N_3O_2$
Theoretical values C:54.73, H:2.62, N:13.67
Found values C:54.69, H:2.53, N:13.58

Example 40.

To a solution of 2.6 g of 2-(m-fluoroanilino)nicotinethylamide in 25 ml of tetrahydrofuran was added 0.48 g of 50% sodium hydride. The mixture was stirred for 30 minutes at room temperature, and 5.4 g of ethyl chlorocarbonate was then added dropwise under cooling. The solution was then refluxed for 10 hours. The solvents were distilled off under reduced pressure and to the residue was added water. The crystals obtained were recrystallized from methanol to give 1.3 g of colorless prisms of 1-(m-fluorophenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 164—165°C
Ultimate analysis value $C_{15}H_{12}FN_3O_2$
Theoretical values C:63.15, H:4.24, N:14.73
Found values C:63.08, H:4.11, N:14.64

Example 41.

To a solution of 3.1 g of 2-(m-trifluoromethylanilino)nicotinethylamide in 25 ml of tetrahydrofuran were added 1.1 g of 50% sodium hydride, and the mixture was stirred for 30 minutes at room temperature. Then a solution of 30% phosgene and toluene was slowly added dropwise to the mixture under cooling, and the solution was stirred for one hour at room temperature. The solvents were distilled off under reduced pressure and to the residue was added water. The crystals obtained were recrystallized from methanol to give 2.9 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 160—161°C
Ultimate analysis value $C_{16}H_{17}F_3N_3O_2$
Theoretical values C:57.31, H:3.61, N:12.53
Found values C:57.60, H:3.59, N:12.42

Example 42.

To a solution of 3.1 g of ethyl 2-(m-trifluoromethylanilino)nicotinate in 20 ml of dimethylformamide was added 0.4 g of 55% sodium hydride and the mixture was stirred for one hour at room temperature. 10.3 g of N-methyl urethan were added and reaction was allowed to occur for 20 hours at 100°C. The precipitate was filtered off, the filtrate was concentrated under reduced pressure and water was added to the residue. The crystals obtained were recrystallized from methanol to yield 1.9 g of colorless prisms of 1-(m-trifluoromethylphenyl)-3-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 224—225°C
Ultimate analysis value $C_{15}H_{10}F_3N_3O_2$
Theoretical values C:56.08, H:3.14, N:13.08
Found values C:56.12, H:3.10, N:13.06

Example 43.

To a solution of 2.76 g of ethyl 2-(m-chloroanilino)nicotinate in 20 ml dimethylformamide was added 0.48 g of 50% sodium hydride and the mixture was stirred for one hour at room temperature. 6 g of urea was further added and reaction was allowed to occur for 15 hours at 160°C. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. To the residue was added water and the crystals obtained were recrystallized from methanol to yield 1.8 g of colorless needles of 1-(m-chlorophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 247—248°C
Ultimate analysis value $C_{13}H_8ClN_3O_2$
Theoretical values C:57.05, H:2.95, N:15.35
Found values C:57.01, H:2.93, N:15.38

Example 44.

To a solution of 2.6 g of ethyl 2-(m-fluoroanilino)nicotinate in 20 ml of dimethylformamide was added 0.48 g of 55% sodium hydride and the mixture was stirred for one hour at room temperature. 8.9 g of urethane was further added and the mixture was refluxed for 15 hours. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. To the residue was added water and the crystals obtained were recrystallized from methanol to give 1.6 g of colorless prisms of 1-(m-fluorophenyl)-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point above 315°C
Ultimate analysis value $C_{13}H_8FN_3O_2$
Theoretical values C:60.71, H:3.14, N:16.33
Found values C:60.72, H:3.02, N:16.36

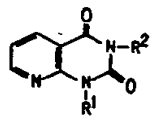
Example 45.

To a solution of 2.8 g of ethyl 2-(m-chloroanilino)nicotinate in 20 ml of dimethyl formamide was added 0.48 g of 55% sodium hydride, and the mixture was stirred for one hour at room temperature. 11.7 g of N-ethyl urethane was further added to the mixture, which then reacted for 15 hours at 100°C. The precipitate was filtered and the filtrate was concentrated under reduced pressure. To the residue was added water and the crystals obtained were recrystallized from methanol to give 1.8 g of colorless prisms of 1-(m-chlorophenyl)-3-ethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione.

Melting point 176—177°C
Ultimate analysis value $C_{15}H_{12}ClN_3O_2$
Theoretical values C:59.71, H:4.01, N:13.92
Found values C:59.69, H:3.99, N:13.89

WHAT WE CLAIM IS:—

1. A compound of the general formula [A]:



[A]

wherein R^1 is an aryl or aralkyl group or a cyclohexyl radical, and R^2 is selected from a hydrogen atom and alkyl, substituted alkyl, unsaturated hydrocarbon, alkoxycarbonyl and substituted unsaturated hydrocarbon groups.

2. A compound as claimed in claim 1, wherein R^1 is
   (1) a phenyl radical, or
   (2) a phenyl radical substituted with
      (a) one or two halogen atoms, or
      (b) one or two lower alkyl groups, or
      (c) a halogen atom and a lower alkyl group, or
      (d) a lower alkoxy group, or
      (e) one or two trifluoromethyl radicals, or
   (3) a benzyl radical, or
   (4) a halogen-substituted benzyl radical, or
   (5) a cyclohexyl radical.

3. A compound as claimed in claim 1 or 2, wherein R^2 is (1) a hydrogen atom, or
   (2) a lower alkyl group, or
   (3) a lower alkyl group substituted with
      (a) a halogen atom, or
      (b) one or two hydroxyl radicals, or
      (c) a lower alkanoyloxy group, or
      (d) a lower alkoxy group, or
      (e) a vinyloxy radical, or
      (f) a hydroxyl lower alkoxy group, or

(g) a phenyl radical, or
(h) a halogen-substituted phenyl radical, or
(i) a lower alkanoyl group, or
(j) a halogen-substituted benzoyl radical, or
(k) a nicotinoyl radical, or
(l) a carboxyl radical, or
(m) a lower alkoxycarbonyl group, or
(n) a carbamoyl radical, or
(o) a cyano radical, or
(p) a di-(lower alkyl) amino group, or
(q) a six-membered cyclicamino group, or
(r) a six-membered cyclicaminocarbonyl group, or
(s) a ureido radical, or
(t) a halogen atom and a hydroxyl radical, or
(u) a halogen atom and a lower alkoxy group, or
(v) a hydroxyl radical and a phenyl radical, or
(w) a hydroxyl radical and a six-membered cyclicamino group, or

(4) a lower alkenyl group, or
(5) a halogen-substituted lower alkenyl group, or
(6) a lower alkynyl group, or
(7) a lower alkoxycarbonyl group, or
(8) a 2,3-epoxypropyl radical.

4. A compound as claimed in any preceding claim, wherein R^1 is selected from phenyl, o-fluorophenyl, m-fluorophenyl, o-chlorophenyl, m-chlorophenyl, m-bromophenyl, m-iodophenyl, o-tolyl, m-tolyl, p-ethoxyphenyl, 2,3-xylyl, 2-methyl-3-chlorophenyl, 3,4-dichlorophenyl, m-trifluoromethylphenyl, p-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, benzyl, p-chlorobenzyl and cyclohexyl.

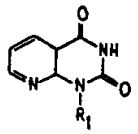
5. A compound as claimed in any preceding claim, wherein R^2 is selected from hydrogen atom, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, 2-chloroethyl, 2-bromoethyl, 3-chloropropyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 2-hydroxy-3-chloropropyl, 2-acetoxyethyl, methoxymethyl, ethoxymethyl, 2-ethoxyethyl, 2-vinyloxyethyl, 2-(2-hydroxyethoxy)ethyl, benzyl, m-chlorobenzyl, phenethyl, acetonyl, p-chlorophenacyl, nicotinoylmethyl, carboxymethyl, 1-carboxyethyl, ethoxycarbonylmethyl, 1-ethoxycarbonylethyl, carbamoylmethyl, cyanomethyl, 2-diethylaminoethyl, 3-dimethylaminopropyl, 2-piperidinoethyl, 2-(3-piperidino)ethyl, 2-(4-methylpiperazino)ethyl, 2-(4-phenylpiperazino)ethyl, 2-(4-benzylpiperazino)ethyl, 2-[4-(2-hydroxyethyl)piperazino)ethyl, 4-(2-hydroxyethyl)piperazinocarbonylmethyl, 2 ureidoethyl, 2-chloro-2-ethoxyethyl, 2-hydroxyphenethyl, 2-hydroxy-3-piperidinopropyl, allyl, 2-methylallyl, 3-chloroallyl, propargyl, ethoxycarbonyl, and 2,3-epoxypropyl.

6. A salt of the compound claimed in any preceding claim.

7. A salt as claimed in claim 6, selected from the hydrochloride, sulfate, phosphate, acetate, benzoate, lactate, succinate, citrate, tartrate, fumarate, malonate and maleate.

8. A fatty acid derivative of a compound of general formula (5).

9. A method of preparing a compound of the general formula [A], comprising reacting a compound of the general formula (1):



(1)

wherein R_1 is the same as in formula [A], with a compound selected from those of the general formulae (2), (4), (6), (8) and (10):

R^2X (2) $\quad$ $Y-CHR^4$ (R^3) (4)

$(R^5O)_2Z$ (6) $\quad$ CH_2-CH-R^6 (W) (8) $\quad$ R^7N_2 (10)

wherein R^2 is the same as in the formula [A], X denotes a halogen atom or an arylsulfonyloxy group, R^3 denotes a hydrogen atom or a lower alkyl group, R^4 denotes a carbamoyl, cyano radical or an alkoxycarbonyl group, Y denotes a halogen atom, R^5 denotes a lower alkyl, substituted alkyl or unsaturated hydrocarbon group, Z denotes a carbonyl (—CO—), sulfonyl ($—SO_2—$) or oxalyl (—CO—CO—) group, R^6 denotes a hydrogen atom, a lower alkyl, halogenated lower alkyl, lower unsaturated hydrocarbon or aryl group, W denotes an oxo (—O—), carbonyldioxo (—O—CO—O—) or sulfinyldioxo (—O—SO—O—) group, and R^7 denotes a lower alkyl group.

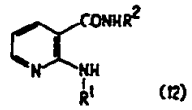
10. A method as claimed in claim 9, wherein the reaction is carried out in an organic solvent.

11. A method as claimed in claim 10, wherein the solvent is selected from toluene, xylene, tetrahydrofuran, dioxane and dimethylformamide.

12. A method as claimed in claim 9, 10 or 11, wherein the reactions involving the compounds of general formulae (2), (4) and (6) are carried out in the presence of a metallic substance or an alkali hydroxide or carbonate.

13. A method as claimed in claim 12, wherein the metallic substance is selected from sodium alcoholate, sodium amide and sodium hydride.

14. A method of preparing a compound of the general formula [A], comprising reacting a compound of the general formula (12)



(12)

wherein R^1 and R^2 are the same as in formula [A], with a compound of the general formula (13):

ACOB (13)

wherein A and B may be the same or different and each represents a halogen atom, a lower alkoxy or amino group, or an imidazolyl radical.

15. A method as claimed in claim 14, wherein the reaction is carried out in an organic solvent.

16. A method as claimed in claim 15, wherein the organic solvent is selected from dimethylformamide, diglyme, tetrahydrofuran, and alcohols.

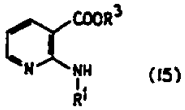
17. A method as claimed in claim 14, 15 or 16, wherein the reaction is carried out in the presence of a metallic substance or an organic base or an inorganic base.

18. A method as claimed in claim 17, wherein the metallic substance is selected from sodium, sodium amide and sodium hydride.

19. A method as claimed in claim 17, wherein the organic base is pyridine or trialkylamine.

20. A method as claimed in claim 17, wherein the inorganic base is an alkali hydroxide or carbonate.

21. A method of preparing a compound of the general formula [A], comprising reacting a compound of the general formula (15):



(15)

wherein R^1 is the same as in the formula [A] and R^3 is the same as in formula (4), with a compound of the general formula (16):

$R^8 NHCOR^9$ (16)

wherein R^8 denotes a hydrogen atom, or a lower alkyl or lower unsaturated hydrocarbon group and R^9 denotes an amino or lower alkoxy group.

22. A method as claimed in claim 21, wherein the reaction is carried out in an organic solvent.

23. A method as claimed in claim 22, wherein the organic solvent is selected from dimethylformamide, diglyme, tetrahydrofuran and alcohols.

24. A method as claimed in 21, 22 or 23, wherein the reaction is carried out in the presence of a metallic substance or an organic base or an inorganic base.

25. A method as claimed in claim 24, wherein the metallic substance is selected from sodium, sodium amide and sodium hydride.

26. A method as claimed in claim 24, wherein the organic base is pyridine or trialkylamine.

27. A method as claimed in claim 24, wherein the inorganic base is an alkali hydroxide or carbonate.

28. A method of preparing a compound of the general formula [A], substantially as hereinbefore described with reference to any one of the Examples.

29. A compound of the general formula [A], whenever prepared by the method of any one of claims 9 to 28.

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